REMARKS

The courtesy of Examiner Misook Yu in conducting an interview with the undersigned on January 25, 2005 is gratefully acknowledged. The Interview Summary which issued at the interview accurately reflects what transpired at the interview as amplified below.

At the interview, Applicant discussed Chaplin et al, the primary reference cited in the section 103 rejections of record, and contended that, from Chaplin et al, one of skill in the art would not have had even a reasonable expectation of success that a NOS inhibitor could augment (rather than decrease) the effect of a tubulin binding agent that is used to cause damage to neovasculature. In particular, Applicant called the Examiner's attention to the portions of Chaplin et al which teach that the proper therapeutic approach to treating a tumor could be either to increase or to decrease blood flow selectively to the tumor (Chaplin at paragraph bridging pages 151-152) and the criticality of being able to predict which approach would be appropriate (Chaplin at page 157, second paragraph). A fuller discussion of the reference follows next.

The paper is split into two sections:

(i) Reversible modulation of tumor blood flow, primarily using vasoactive drugs. These approaches could be used to **either increase or decrease** blood flow selectively to the tumor. The potential benefits of transiently increased tumor blood flow described are improved delivery of systemic agents and improved oxygenation. The potential benefits of transiently decreased blood flow described are (a) enhancing the activity of agents that

are more toxic in a hypoxic or acidic environment, and (b) manipulating drug pharmacookinetics, i.e. to increase the exposure time of tumor cells to anti-cancer agents. (ii) Irreversible reduction in tumor blood flow caused by vascular targeting agents, resulting in prolonged ischaemia and extensive tumor cell death.

From this paper one of skill in the art could not predict whether there would be a benefit (as opposed, for example, to a detriment) of combining a vascular targeting agent which causes irreversible reductions in tumor blood flow, with a NOS inhibitor, which under some (but not all) conditions may act as a reversible inhibitor of tumor blood flow.

At the interview, Applicant also discussed the publications and paper that were cited in the Information Disclosure Statement filed on January 14, 2005, and contended that these provide evidence of unexpectedly good results that should be sufficient to show the patentability of claims to the combination of tubulin binding agent and NOS inhibitor--even assuming for the sake of argument that the cited art set forth a *prima facie* case of alleged obviousness (which Applicant contended it does not). As discussed in the interview, the Tozer et al and Davis et al publications show the potentiating effect of combining Combretastatin A4 with a range of NOS inhibitors. The Wachsberger et al paper shows that the co-administration of the vascular tubulin binding agent ZD6126 (N-acetylcolchinol-O-phosphate) and the NOS inhibitor L-NNA was able to overcome resistance to ZD 6126 in U87 glioblastoma cells. Table 1 of the paper shows the enhanced tumour necrosis in this model obtained by dosing ZD6126 together with L-NNA. This paper has now been published (Clin. Cancer Res. 2005; 11(2Pt):835-842) and a copy is submitted herewith.

For the reasons discussed at the interview, and above, it is respectfully submitted that the rejections based on Chaplin et al, either alone or in combination with the cited secondary references, are incompetent to set forth even a *prima facie* case of obviousness for the invention as claimed. Moreover, even assuming for the sake of argument that the references were sufficient, it is respectfully submitted that the record shows advantageous results with the claimed combination of components that would be sufficient to rebut any alleged *prima facie* case of obviousness.

With specific respect to the rejection under 35 USC 102(b) on the basis of Bonfoco et al, Applicant respectfully notes that Bonfoco et al do not show, suggest or enable a **pharmaceutical** composition comprising a tubulin binding agent, a nitric oxide inhibitor and a pharmaceutically acceptable excipient. Rather, Bonfoco et al teach away from the formation of a pharmaceutical composition by teaching the necessity of including rat cells in the culture medium described therein. It is respectfully submitted that a pharmaceutical composition cannot comprise rat cells. This is *a fortiori* true with respect to new claim 50 which uses the "consisting essentially of" transitional to preclude components that would materially affect the basic and novel properties of the claimed composition (see MPEP Section 2111.03). The inclusion of rat cells would preclude the use of the composition for the basic use described in the specification.

The claims have been amended to define the amounts of the components in functional terms and to remove the bases for the claim objections and for the rejections under 35 USC 112, second paragraph. All claims as amended are respectfully believed to be sufficiently definite to satisfy the dictates of 35 USC 112, second paragraph.

In view of the above, it is respectfully submitted that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

CLIFFORD J. MASS
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.30,086(212)708-1890